 Isothiourea-Mediated One-Pot Synthesis of Trifluoromethyl Substituted 2-Pyrones

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Supporting Information Placeholder

ABSTRACT: A one-pot isothiourea-mediated Michael addition/lactonization/thiol elimination cascade sequence for the formation of 4,6-disubstituted and 3,4,6-trisubstituted 2-pyrones from (phenylthio)acetic acids and α,β-unsaturated trifluoromethyl ketones is described. The synthesis of a COX-2 inhibitor and the wide-ranging derivatization of the 2-pyrene moiety to trifluoromethyl substituted aromatics and heteroaromatics is also disclosed.

2-Pyrones are a class of unsaturated heterocycle that is extremely prevalent in Nature, with examples being found in plants, animals, marine organisms, bacteria, fungi and insects. The parent 2-pyrene heterocycle has recently been found to have both cytotoxic and DNA-damaging effects in lung cancer cells. Several examples of the 2-pyrene containing bufadienolide family of bioactive natural products have been isolated from the traditional Chinese medicine Ch’an Su, underlying their potential as therapeutic agents. Alongside their biological importance, 2-pyrones have also found great utility in complex molecule synthesis. Their reactivity towards both nucleophiles and electrophiles has permitted their use in the synthesis of a wide-range of high-value heterocyclic and non-heterocyclic compounds. Despite their synthetic utility there are few routes to 2-pyrones, the most common being the tandem condensation/cyclization of β-ketoesters, and novel catalytic synthetic routes to these heterocycles are of significant interest.

Building upon the seminal work of Romo and co-workers on the in situ activation of carboxylic acids to generate ammonium enolates, we have demonstrated that isothioureas catalyze the intermolecular Michael addition/lactonization/lactamization of arylacetic acids and electron-deficient Michael acceptors. This concept was further developed by incorporating a suitable leaving group within the acetic acid, allowing the generation of pyridines through a cascade (Michael addition/lactamization/elimination) sequence followed by N- to O-sulfonyl transfer (Scheme 1a). Seeking to further develop this concept, herein we report the successful development of an organocatalyzed synthesis of 2-pyrones, incorporating the pharmaceutically relevant trifluoromethyl substituent at the 6-position (Scheme 1b).

Scheme 1. Isothiourea-mediated One-pot Synthesis of Planar Heterocycles

a) Previous work (ref 11):

b) This work:

1) Isothiourea catalysis
2) PhSH elimination
3) N- to O-sulfonyl transfer

1) Isothiourea catalysis
2) PhSH elimination

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2) PhSH elimination

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2) PhSH elimination

1) Isothiourea catalysis
2) PhSH elimination

1) Isothiourea catalysis
2) PhSH elimination
Our mechanistic rationale for this transformation begins with N-acylation of DHPB (3,4-dihydro-2H-pyrimido[2,1-b]benzothiazole) 1 with mixed anhydride 2, formed in situ from phenyl(thio)acetic acid, pivaloyl chloride and base (Scheme 1c). Deprotonation of 3 affords the (Z)-enolate 4, which would undergo Michael addition to trifluoromethyl enone 5,14. Lactonization via 6 forms dihydroxyphene 7 with concomitant regeneration of DHPB, and rapid off-cycle elimination of thiophenol forms the pyrone 8.

Table 1. Reaction Optimization

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<th>entry</th>
<th>acid</th>
<th>cat. (mol %)</th>
<th>solvent</th>
<th>time (h)</th>
<th>yield (%)</th>
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<td>2</td>
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<td>(52)c</td>
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<td>9a</td>
<td>(13)</td>
<td>CH₂Cl₂</td>
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<td>(34)</td>
</tr>
<tr>
<td>4</td>
<td>9a</td>
<td>(1)</td>
<td>MeCN</td>
<td>24</td>
<td>88 (99)</td>
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<tr>
<td>5</td>
<td>9a</td>
<td>(13)</td>
<td>MeCN</td>
<td>24</td>
<td>50 (55)</td>
</tr>
<tr>
<td>6d</td>
<td>9a</td>
<td>(1)</td>
<td>MeCN</td>
<td>24</td>
<td>72 (84)</td>
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<tr>
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<td>9a</td>
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<td>80</td>
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<tr>
<td>9f</td>
<td>9a</td>
<td>(1)</td>
<td>MeCN</td>
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<tr>
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<td>24</td>
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<tr>
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<td>9c</td>
<td>(1)</td>
<td>MeCN</td>
<td>24</td>
<td>23</td>
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a2 equiv of acid 9a-c.
bIsolated yield, NMR yield in parentheses measured against 1-methyl naphthalene as internal standard. c10 not fully consumed. dReaction conditions: (CH₃)₂CCOCl (2 equiv), i-Pr₂NEt (2 equiv), then 1, 10, i-Pr₂NEt (2 equiv). e1.5 equiv 9a.fOpen flask conditions. g6 mmol 10, 1.30 g pyrone 11 isolated. hReaction in the absence of DHPB 1.

Initially, the reaction of in situ activated (phenylthio)acetic acid 9a with trifluoromethyl enone 10 in the presence of 20 mol % DHPB 1 and excess i-Pr₂NEt gave the desired pyrone 11 in a promising 72% isolated yield (Table 1, entry 1). Alternative Lewis bases resulted in a poor conversion into 11 according to ¹H NMR analysis of the crude reaction mixtures (entries 2 and 3). The reaction solvent was next examined, with MeCN proving superior, giving 11 in 88% isolated yield (entry 4). Attempts to reduce the equivalents of pivaloyl chloride, base, acid 9a or performing the reaction under non-anhydrous conditions resulted in inferior yields of 11 (entries 6-8). The reaction was amenable to scale-up, affording 1.30 g of 1 in 90% yield from 6 mmol of acceptor 10 (entry 9). The catalyst loading could be reduced to 0.1 mol %, resulting in acceptable but lower isolated yields (entries 10 and 11). Surprisingly, a strong background reaction was observed, giving 11 in 59% isolated yield in the absence of isothiourea catalyst, with full consumption of 10 (entry 12). However, DHPB 1 clearly promotes the desired reaction pathway leading to higher isolated yields of 11. Chloro- and bromoacetic acid 9b and 9c were also screened under these conditions, but returned low yields of 11 with full consumption of acceptor 10 (entries 13 and 14).13

Table 2. Reaction Scope: Variation of Trifluoromethyl Enone

<table>
<thead>
<tr>
<th>product</th>
<th>yield (%)</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO₂S₂</td>
<td>57 (95)</td>
<td>Br</td>
<td>73 (95)</td>
</tr>
<tr>
<td>Br</td>
<td>73 (95)</td>
<td>Br</td>
<td>63 (82)</td>
</tr>
<tr>
<td>Br</td>
<td>71 (88)</td>
<td>Br</td>
<td>45 (83)</td>
</tr>
<tr>
<td>O₂N</td>
<td>53 (85)</td>
<td>Br</td>
<td>(69)</td>
</tr>
<tr>
<td>MeO₂S₂</td>
<td>(61)c</td>
<td>Br</td>
<td>89 (99)</td>
</tr>
</tbody>
</table>

cIsolated yield with 1 mol % I, numbers in parentheses refer to isolated yield with 20 mol % I. h72 h reaction

With optimized conditions in hand, a systematic examination of the scope of the reaction with aryl substituted trifluoromethyl enones was conducted, at both 1 and 20 mol % catalyst loading (Table 2). Both electron-poor and -neutral para-substituted aromatics were generally well tolerated, giving high yields of pyrones 14-17 at 20 mol % loading. However, isolated yields with electron-poor aromatics were acceptable but lower at 1 mol % 1. An extended reaction time of 72 h was required for the formation of para-methoxy substituted pyrone 18, even with 20 mol % 1. Halogen substituents at the meta- and ortho-positions (19 and 20) were incorporated without consequence, and heteroaromatic 2-thiophenyl and 2-furanyl substituted pyrones 21 and 22 could also be accessed in satisfactory yields. Finally, the 2-naphthalene substituted pyrone 23 was isolated in excellent yield at both 1 and 20 mol % 1.

The possibility of introducing further substituents through the use of α-substituted (phenylthio)acetic acids to generate 3,4,6-trisubstituted pyrones was then investigated, as α,α-disubstituted acetic acids have proven to be a limiting factor in
our previous work.\textsuperscript{10b} Whilst the reaction of $\alpha$-methyl acid 24 proved sluggish at rt even using 20 mol % of 1, heating the reaction to 95 °C in a sealed tube resulted in a separable mixture of the desired trisubstituted pyrone 26 and a single diastereoisomer of sulfide 25 that were isolated in excellent overall yield (Scheme 2). Sulfide 25 had the expected syn relationship between the C(4)H and the SPh group (as confirmed by single crystal X-ray analysis), which would be unable to undergo anti-periplanar elimination.\textsuperscript{16} To facilitate the desired elimination, exposure of 25 to m-CPBA\textsuperscript{17} delivered pyrone 26 in 91% yield, presumably through syn-elimination of phenylsulfenic acid.\textsuperscript{18} This process could be expedited, with the oxidation carried out directly on the mixture of products isolated after aqueous work-up, affording 26 in good yield. 3-Phenyl pyrone 27 could also be accessed in moderate yield.\textsuperscript{19}

**Scheme 2. 3,4,6-Trisubstituted Pyrone from $\alpha$-Methyl Acid 24**

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{PhS} & \quad \text{OH} \\
\text{CF}_3 & \quad \text{PhS} \\
\text{PhS} & \quad \text{CF}_3 \\
\text{PhS} & \quad \text{CF}_3 \\
\text{PhS} & \quad \text{CF}_3 \\
\text{PhS} & \quad \text{CF}_3 \\
\end{align*}
\]

\text{Conditions}\textsuperscript{\textit{a}}: (CH\textsubscript{3})\textsubscript{2}COCl (3 equiv), i-Pr\textsubscript{2}NEt (2.5 equiv), MeCN, rt, 30 mins; then 1 (20 mol %), i-Pr\textsubscript{2}NEt (2.5 equiv), MeCN, rt, 0.5 h, 64% yield.

To demonstrate the viability of this methodology, its application to a suitable target with established biological activity was investigated. Merck & Co. have examined trifluoromethyl substituted pyrones as COX-2 inhibitors, with 3-phenylthio substituted pyrone 31 a potent example (Scheme 3a).\textsuperscript{20} Bis(phenylthio)acetic acid 29\textsuperscript{11} and acceptor 30 were considered viable precursors to this target, and their reaction generated a separable mixture of pyrones 31 and 14.\textsuperscript{22} To ascertain the origin of the desulfurized by-product 14, control experiments were conducted upon isolated 31. Resubmission of 31 to the reaction conditions (20 mol % 1, i-Pr\textsubscript{2}NEt, MeCN, rt)

**Scheme 3. Synthesis of COX-2 Inhibitor 31**

\[
\begin{align*}
\text{PhS} & \quad \text{O} \\
\text{CF}_3 & \quad \text{PhS} \\
\text{PhS} & \quad \text{CF}_3 \\
\text{PhS} & \quad \text{CF}_3 \\
\text{PhS} & \quad \text{CF}_3 \\
\text{PhS} & \quad \text{CF}_3 \\
\text{PhS} & \quad \text{CF}_3 \\
\end{align*}
\]

\text{Conditions}\textsuperscript{\textit{a}}: PhS (2 equiv), PhS (2 equiv), MeCN, rt, 0.5 h, 64% yield.

\textsuperscript{\textit{a}}Reaction conditions: (CH\textsubscript{3})\textsubscript{2}COCl (3 equiv), i-Pr\textsubscript{2}NEt (3 equiv), MeCN, rt, 0.5 h; then 1 (20 mol %), i-Pr\textsubscript{2}NEt (2.5 equiv), Δ, 24 h.

In conclusion, the concise synthesis of a range of di- and trisubstituted 2-pyrones from (thiophenyl)acetic acids and readily available trifluoromethyl enones via an isothiourea-mediated one-pot Michael addition/lactonization/thiol elimination sequence has been demonstrated. The efficiency of this process allows the synthesis of biologically relevant compounds with high selectivity and yield. Further investigations in our laboratory are directed towards novel applications of isothioureas in catalysis.

**ASSOCIATED CONTENT**

**Supporting Information**

General experimental procedures, characterization data, spectra, and X-ray structure of 25. This material is available free of charge via the Internet at http://pubs.acs.org.
REFERENCES


(2) For a comprehensive review of the isolation, synthesis and reactions of 2-pyrones, see: Goel, A.; Ram, V. J. Tetrahedron 2009, 65, 7865-7913.


(15) Phenylsulfanyl)-2-methoxy- and 2-benzoyloxycarbonyl acid were also tested, but all gave intractable mixtures of products.

(16) See the Supporting Information. CCDC 974564 (25) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


(18) Resubmission of isolated sulfide 25 to the reaction conditions (DHPB 1, i-Pr₂NEt, MeCN, Δ) returned only starting material.

(19) 3-Phenyl substituted pyrone 27 was isolated along with the dihydropyrene 28, presumably resulting from thiophenol-mediated desulfurization of the phenyl analogue of sulfide 25, and tautomeraisation. See the Supporting Information for details.
Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title, should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem, etc., that is discussed in the manuscript. Consult the journal’s Instructions for Authors for TOC graphic specifications.